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WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :  A01N 63/00		A1	(11) International Publication Number: <b>WO 98/47374</b>  (43) International Publication Date: 29 October 1998 (29.10.98)
(21) International Application Number: PCT/US98/07307  (22) International Filing Date: 10 April 1998 (10.04.98)		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(30) Priority Data: 60/044,643 18 April 1997 (18.04.97) US  (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/044,643 (CIP) Filed on 18 April 1997 (18.04.97)		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(71) Applicant (for all designated States except US): GANEDEN BIOTECH, INC. [US/US]; 8738-6 Villa La Jolla Drive, La Jolla, CA 92037 (US).  (72) Inventors; and (75) Inventors/Applicants (for US only): FARMER, Sean [US/US]; 8738-6 Villa La Jolla Drive, La Jolla, CA 92037 (US). MIKHAIL, Robert, J. [US/US]; 1493-B E. Lexington Avenue, El Cajon, CA 92019 (US).  (74) Agent: FITTING, Thomas; Suite 300, 12526 High Bluff Drive, San Diego, CA 92130 (US).			

(54) Title: TOPICAL USE OF PROBIOTIC BACILLUS SPORES TO PREVENT OR CONTROL MICROBIAL INFECTIONS

## (57) Abstract

Compositions including an isolated *Bacillus* species, spores or an extracellular product of *B. coagulans*, suitable for topical application, for inhibiting growth of yeast, fungus, bacteria or Herpes simplex virus are disclosed. Methods of inhibiting growth of yeast, fungus, bacteria or Herpes simplex virus by topical application of compositions that include an isolated *Bacillus* species, spores or an extracellular product of a *B. coagulans* strain are disclosed.

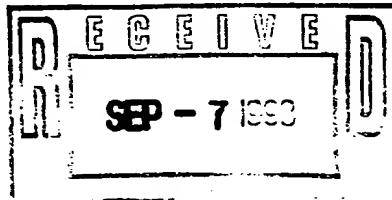
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From the INTERNATIONAL SEARCHING AUTHORITY

To: THOMAS FITTING  
12526 HIGH BLUFF DRIVE  
SUITE 300  
SAN DIEGO, CA 92130



PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference GB10004P	Date of Mailing (day/month/year) <b>31 AUG 1993</b>
International application No. PCT/US98/07307	International filing date (day/month/year) 10 APRIL 1998
Applicant GANEDEN BIOTECH, INC.	

1.  The applicant is hereby notified that the international search report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO

34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer  
VERA AFREMOVA

Telephone No. (703) 308-0196

(See notes on accompanying sheet)

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GBI0004P	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US98/07307	International filing date (day/month/year) 10 APRIL 1998	(Earliest) Priority Date 18 APRIL 1997
Applicant GANEDEN BIOTECH, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1.  Certain claims were found unsearchable (See Box I).
2.  Unity of invention is lacking (See Box II).
  - filed with the international application.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
    - transcribed by this Authority.
3.  The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - the text is approved as submitted by the applicant.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
    - transcribed by this Authority.
4. With regard to the title,
  - the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - the text is approved as submitted by the applicant.
  - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
 

Figure No. \_\_\_\_\_

  - as suggested by the applicant.
  - because the applicant failed to suggest a figure.
  - because this figure better characterizes the invention.
  - None of the figures.

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) A01N 63/00

US CL 424/93.46

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.46

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, WPIDS, MEDLINE, AGRICOLA, CA

search terms: *Bacillus* sp., *Bacillus coagulans*, probiotic, topical application, skin or mucous membrane colonization.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/14187 A1 (CONSIGLIO NAZIONALE DELLE RICERCHE) 22 July 1993, column 3, lines 10-14, 30-35, examples 2-3.	1-5,44
Y		7-9,14-24
X	US 5,000,939 A (DRING et al.) 19 March 1991, column 1, lines 25-30, column 3, lines 55-60, column 4, lines 4-6, examples 1-9.	10-12, 44
Y		13, 25-27
X	US 5,045,314 A (BONE et al.) 03 September 1991, column 3, lines 24-26, 56-65, column 4, line 9.	1,3,4,44
Y		2,5-9,14-24

 Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 JUNE 1998

Date of mailing of the international search report

31 AUG 1998

Name and mailing address of the ISA/US  
Commissioner of Patents and Trademarks  
Box PCT  
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

VERA AFREMOVA

Telephone No. (703) 308-0196

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,871,539 A (HATA et al.) 03 October 1989, column 9, lines 16, 37-39, 65, column 10, lines 23-25, 34-37, column 11, lines 20-29, column 20, lines 59-61, column 21, lines 60-65, tables 4-6.	1-4, 28, 29, 44 -----
Y		5-9, 14-24, 30-43
X	JP 63-96107 A (SHISEIDO CO LTD) 27 April 1988, abstract.	1, 3, 9, 44 -----
Y		2, 4-8, 14-24
X	SIEGEL et al. Clearance of bacillus sphaericus and Bacillus thuringiensis ssp. israelensis from mammals. Journal of Economic Entomology. April 1990, Vol. 83, No. 2, pages 347-355, especially pages 349-350.	1,5,14,17 -----
Y		6-9,15,16, 18-24
X	SYTKNIK, S.I. Antagonistic action of corinebacteria and bacilli of cutaneous ecotype on staphylococci. Mikrobiologicheskii Zhurnal. January-February 1989, Vol. 51, No. 1, pages 82-87, especially page 86.	1,2,4 -----
Y	US 5,431,924 A (GHOSH et al.) 11 July 1995, abstract.	3,5-9, 14-24 13, 27
Y	SCHOENI et al. Inhibition of Campylobacter jejuni colonization in chicks by defined competitive exclusion bacteria. Applied and Environmental Microbiology. April 1994, Vol.60, No.4, pages 1191-1197, abstract.	6-8, 20-22, 31, 32, 41-43

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s)1-9, 14-24 and 44, drawn to a probiotic composition with living culture of *Bacillus* species, a method of inhibiting microbial growth with the probiotic composition and a therapeutic system.

Group II, claim(s) 10-13 and 25-27, drawn to a composition with an extracellular product of *Bacillus coagulans* and a method for inhibiting microbial growth with the composition.

Group III, claim(s) 28-43, drawn to an article of manufacture impregnated with *Bacillus* species and a method of inhibiting microbial growth with an article of manufacture.

The inventions listed as Groups I, II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The unifying technical feature of Group I is the presence of a *Bacillus* species in a pharmaceutically acceptable carrier.

The special technical feature of Group II is the presence of an extracellular product of *Bacillus coagulans* in a pharmaceutical carrier.

The special technical feature of a Group III is a flexible article of manufacture with an effective amount of *Bacillus* species.

Compositions of Groups I, II and III are distinct because they have different components such as a living probiotic culture or an extracellular product free from living culture or an article of manufacture impregnated with an effective amount of *Bacillus* species.

The prior art demonstrates the pharmaceutical compositions with *Bacillus* species for treating diseases of animals, for example: US Pat. 5,455,028.

PCT does not provide for multiple compositions under PCT Rule 13.1-13.3.

U41504154  
430 Rec'd PCT/PTO 22 MAR 2000

**CHAPTER I**  
**PCT TELEPHONE MEMORANDUM**  
**FOR**  
**LACK OF UNITY OF INVENTION**



PCT No.: PCT/US98/07307

Examiner: VERA AFREMOVA

Attorney spoken to: THOMAS FITTING

Date of call: 19 JUNE 1998

- Amount of payment approved: \$420.00
- Deposit account number to be charged: 06-1175
- Attorney elected to pay for ALL additional inventions
- Attorney elected to pay only for the additional inventions covered by
  - Group(s):  
- encompassing -
  - Claim(s):
    - Attorney elected **NOT** to pay for any additional inventions, therefore, only the first claimed invention (Group I) covered by Claim(s)    has been searched.
    - Attorney was orally advised that there is no right to protest for any group not paid for.
    - Attorney was orally advised that any protest must be filed no later than 15 days from the mailing of the Search Report (PCT/ISA/210).

**Time Limit For Filing A Protest**

Applicant is hereby given 15 days from the mailing date of this Search Report in which to file a protest of the holding of lack of unity of invention. In accordance with PCT Rule 40.2, applicant may protest the holding of lack of unity only with respect to the group(s) paid for.

**Detailed Reasons For Holding Lack Of Invention:**

**Detailed Reasons For Holding Lack of Unity Of Invention:**  
*(Continued on a separate sheet)*

**Note: A copy of this form must be attached to the Search Report.**

09/509159

430 Rec'd OCT 7 TO 22 MAR 2000  
International Application No.: PCT/US98/07307

**ATTACHMENT TO CHAPTER I PCT TELEPHONE MEMORANDUM  
FOR  
LACK OF UNITY OF INVENTION**

**Detailed Reasons For Holding Lack Of Unity Of Invention:**

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-9, 14-24 and 44, drawn to a probiotic composition with living culture of *Bacillus* species, a method of inhibiting microbial growth with the probiotic composition and a therapeutic system.

Group II, claim(s) 10-13 and 25-27, drawn to a composition with an extracellular product of *Bacillus coagulans* and a method for inhibiting microbial growth with the composition.

Group III, claim(s) 28-43, drawn to an article of manufacture impregnated with *Bacillus* species and a method of inhibiting microbial growth with an article of manufacture.

The inventions listed as Groups I, II and III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The unifying technical feature of Group I is the presence of a *Bacillus* species in a pharmaceutically acceptable carrier.

The special technical feature of Group II is the presence of an extracellular product of *Bacillus coagulans* in a pharmaceutical carrier.

The special technical feature of a Group III is a flexible article of manufacture with an effective amount of *Bacillus* species.

Compositions of Groups I, II and III are distinct because they have different components such as a living probiotic culture or an extracellular product free from living culture or an article of manufacture impregnated with an effective amount of *Bacillus* species.

The prior art demonstrates the pharmaceutical compositions with *Bacillus* species for treating diseases of animals, for example: US Pat. 5,455,028.

PCT does not provide for multiple compositions under PCT Rule 13.1-13.3.

## NOTES TO FORM PCT/ISA/220 (continued)

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

The statement should be brief, it should not exceed 500 words if in English or if translated into English.

It should not be confounded with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It should not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### In what language?

The amendments must be made in the language in which the international application is published. The letter and any statement accompanying the amendments must be in the same language as the international application if that language is English or French; otherwise, it must be in English or French, at the choice of the applicant.

### Consequence if a demand for international preliminary examination has already been filed?

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase?

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.